

# Contents

## **INTRODUCTION**

**Cells as macromolecular assemblies** 1

## **CHAPTER 1**

**3**

**Cells obey the laws of  
physics and chemistry**

Macromolecules are assembled by polymerizing small molecules 6  
Proteins consist of chains of amino acids 9  
Protein conformation depends upon the aqueous environment 14  
Protein structures are extremely versatile 18  
How do proteins fold into the correct conformation? 21

## **CHAPTER 2**

**29**

**Cells are organized into  
compartments**

Cellular compartments are bounded by membranes 31  
The cytoplasm contains networks of membranes 37  
Cell shape is determined by the cytoskeleton 40  
Some organelles are surrounded by an envelope 43  
The environment of the nucleus and its reorganization 46  
The role of chromosomes in heredity 48

<b>PART 1</b>	<b>DNA as a store of information</b>	<b>57</b>
<b>CHAPTER 3</b>		<b>59</b>
<b>Genes are mutable units</b>	Discovery of the gene	62
	Genes lie in a linear array on chromosomes	65
	One gene—one protein: the basic paradigm	70
	A modern definition: the cistron	72
	Mapping mutations at the molecular level	74
	The nature of multiple alleles	76
<b>CHAPTER 4</b>		<b>81</b>
<b>DNA is the genetic material</b>	The discovery of DNA	82
	DNA is the (almost) universal genetic material	84
	The components of DNA	87
	DNA is a double helix	91
	DNA replication is semiconservative	94
	The genetic code is read in triplets	98
	Mutations change the sequence of DNA	101
	Mutations are concentrated at hotspots	105
	The rate of mutation	106
<b>CHAPTER 5</b>		<b>109</b>
<b>The topology of nucleic acids</b>	DNA can be denatured and renatured	110
	Nucleic acids hybridize by base pairing	111
	Single-stranded nucleic acids may have secondary structure	115
	Inverted repeats and secondary structure	117
	Duplex DNA has alternative double-helical structures	119
	Closed DNA can be supercoiled	122
	Supercoiling influences the structure of the double helix	124
<b>CHAPTER 6</b>		<b>127</b>
<b>Isolating the gene</b>	A restriction map can be constructed by cleaving DNA into specific fragments	129
	Restriction sites can be used as genetic markers	134
	Obtaining the sequence of DNA	142
	Prokaryotic genes and proteins are colinear	146
	Eukaryotic genes can be interrupted	149
	Some DNA sequences code for more than one protein	151
	Genetic information can be provided by DNA or RNA	154
	The scope of the paradigm	157

**PART 2****Translation: expressing genes as proteins 161****CHAPTER 7 163****The assembly line for protein synthesis**

Transfer RNA is the adaptor	165
Messenger RNA is translated by ribosomes	167
The meaning of the genetic code	171
The ribosomal sites of action	174
Initiation in bacteria needs 30S subunits and accessory factors	176
A special initiator tRNA starts the polypeptide chain	179
Eukaryotic initiation involves many factors	183
Elongation factor T brings aminoacyl-tRNA into the A site	185
Translocation moves the ribosome	188
Finishing off: three codons terminate protein synthesis	192

**CHAPTER 8 197****Transfer RNA is the translational adaptor**

The universal cloverleaf	198
The tertiary structure is L-shaped	200
Synthetases fall into two classes that recognize similar features in tRNA	202
Discrimination in the charging step	207
Codon-anticodon recognition involves wobbling	211
tRNA contains many modified bases	213
Base modification may control codon recognition	215
The genetic code is altered in ciliates and mitochondria	217
Suppressor tRNAs have mutated anticodons that read new codons	219
tRNA may influence the reading frame	224
tRNA transcripts are cut and trimmed from clusters by several enzymes	227

**CHAPTER 9 233****Ribosomes provide a translation factory**

Ribosomes are compact particles in which most proteins interact with rRNA	234
Subunit assembly is linked to topology	239
The role of ribosomal RNA in protein synthesis	242
Ribosomes have several active centers	246
The accuracy of translation	249

**CHAPTER 10 253****Messenger RNA is the template**

The lifecycle of messenger RNA	254
Most bacterial genes are expressed via polycistronic messengers	258

The translation of eukaryotic mRNA	262
Most eukaryotic mRNAs are polyadenylated at the 3' end	264
All eukaryotic mRNAs have a methylated cap at the 5' end	266
Initiation involves base pairing between mRNA and rRNA	268
Small subunits migrate to initiation sites on eukaryotic mRNA	270
Processing is necessary to produce some RNAs	271
Stability of mRNA is determined by particular sequences	273

**PART 3****Constructing the cell 277****CHAPTER 11 279****The apparatus for protein localization**

Post-translational membrane insertion depends on leader sequences	282
Leaders determine protein location within mitochondria and chloroplasts	285
Signal sequences link protein synthesis to membranes during co-translational transfer	289
Anchor sequences cause proteins to be retained in membranes	294
Bacterial proteins are transported by both co-translational and post-translational mechanisms	298
Oligosaccharides are added to proteins in the endoplasmic reticulum and Golgi	300
Coated vesicles transport both exported and imported proteins	305
Protein localization depends on further signals	314

**CHAPTER 12 319****Receptors and signal transduction: channels and ion uptake**

A more detailed view of the plasma membrane	323
Receptors recycle via endocytosis	326
Protein tyrosine kinases induce phosphorylation cascades	331
G proteins may activate or inhibit target proteins	334
Carriers and channels form water-soluble paths through the membrane	336
Pores control nuclear ingress and egress	342

**CHAPTER 13 349****Cell cycle and growth regulation**

Replication and mass cycles are coordinated	351
Regulatory activities are found at S phase and at M phase	353
M-phase kinase is a dimer that regulates entry into mitosis	355
Protein phosphorylation and dephosphorylation control the cell cycle	359
p34 is the key regulator in yeasts	361
CDC28 acts at both START and mitosis in <i>S. cerevisiae</i>	367
What controls the G1-S transition?	369

**PART 4**

	<b>Control of prokaryotic gene expression</b>	<b>375</b>
<b>CHAPTER 14</b>		<b>377</b>
<b>Control at initiation: RNA polymerase–promoter interactions</b>	Transcription is catalyzed by RNA polymerase	379
	Bacterial RNA polymerase consists of core enzyme and sigma factor	383
	Sigma factor controls binding to DNA	387
	Promoter recognition depends on consensus sequences	393
	RNA polymerase binds to one face of DNA	396
	Substitution of sigma factors may control initiation	401
	Sporulation utilizes a cascade of many sigma factors	404
<b>CHAPTER 15</b>		<b>413</b>
<b>A panoply of operons: the lactose paradigm and others</b>	Structural gene clusters are coordinately controlled	415
	The activity of repressor protein is controlled by a small molecule inducer	418
	Mutations identify the operator and the regulator gene	421
	Repressor protein binds to the operator and is released by inducer	427
	The specificity of protein–DNA interactions	432
	Repression can occur at multiple loci	435
	Distinguishing positive and negative control	437
	Catabolite repression involves positive regulation at the promoter	439
	Autogenous control may occur at the level of translation	445
	Hard times provoke the stringent response	450
<b>CHAPTER 16</b>		<b>457</b>
<b>Control by RNA structure: termination and antitermination</b>	Bacterial RNA polymerase has two modes of termination	460
	How does rho factor work?	462
	Antitermination depends on specific sites	465
	More subunits for RNA polymerase	470
	Alternative secondary structures control attenuation	473
	Small RNA molecules can regulate translation	479
	Regulation by cleavage of mRNA	482
	Cleavages are needed to release prokaryotic and eukaryotic rRNAs	484
<b>CHAPTER 17</b>		<b>491</b>
<b>Phage strategies: lytic cascades and lysogenic repression</b>	Lytic development is controlled by a cascade	494
	Functional clustering in phages T7 and T4	496
	The lambda lytic cascade relies on antitermination	499
	Lysogeny is maintained by an autogenous circuit	503

The DNA-binding form of repressor is a dimer	506
Repressor binds cooperatively at each operator using a helix-turn-helix motif	508
How is repressor synthesis established?	515
A second repressor is needed for lytic infection	519
A delicate balance: lysogeny versus lysis	521

<b>PART 5</b>	<b>Perpetuation of DNA</b>	<b>525</b>
<b>CHAPTER 18</b>		<b>527</b>
<b>The replicon: unit of replication</b>	Origins can be mapped by autoradiography and electrophoresis	529
	The bacterial genome is a single replicon	532
	Each eukaryotic chromosome contains many replicons	535
	Isolating the origins of yeast replicons	537
	D loops may be maintained at mitochondrial origins	539
	The problem of linear replicons	540
	Rolling circles produce multimers of a replicon	544
	Single-stranded genomes are generated for bacterial conjugation	549
	Connecting bacterial replication to the cell cycle	553
	Cell division and chromosome segregation	555
	Multiple systems ensure plasmid survival in bacterial populations	560
	Plasmid incompatibility is connected with copy number	563
<b>CHAPTER 19</b>		<b>571</b>
<b>Primosomes and replisomes: the apparatus for DNA replication</b>	DNA polymerases: the enzymes that make DNA	572
	DNA synthesis is semidiscontinuous and primed by RNA	579
	The primosome initiates synthesis of Okazaki fragments	582
	Coordinating synthesis of the lagging and leading strands	586
	The replication apparatus of phage T4	592
	Creating the replication forks at an origin	594
	Common events in priming replication at the origin	597
	Does methylation at the origin regulate initiation?	600
<b>CHAPTER 20</b>		<b>605</b>
<b>Systems that safeguard DNA</b>	The consequences of modification and restriction	606
	Type II restriction enzymes are common	608
	The alternative activities of type I enzymes	609
	The dual activities of type III enzymes	613
	Dealing with injuries in DNA	614
	Excision–repair systems in <i>E. coli</i>	618
	Controlling the direction of mismatch repair	621
	Retrieval systems in <i>E. coli</i>	623
	An SOS system of many genes	625
	Mammalian repair systems	628



**PART 6****Organization of the eukaryotic genome 631****CHAPTER 21 633****The extraordinary power of DNA technology**

Any DNA sequence can be cloned in bacteria or yeast	634
Constructing the chimeric DNA	636
Copying mRNA into cDNA	640
Isolating individual genes from the genome	642
Walking along the chromosome	647
Eukaryotic genes can be expressed in prokaryotic systems	652

**CHAPTER 22 657****Genome size and genetic content**

The C-value paradox describes variations in genome size	658
Reassociation kinetics depend on sequence complexity	660
Eukaryotic genomes contain several sequence components	663
Nonrepetitive DNA complexity can estimate genome size	664
Eukaryotic genomes contain repetitive sequences that are related but not identical	666
Most structural genes lie in nonrepetitive DNA	668
How many nonrepetitive genes are expressed?	671
Genes are expressed at widely varying levels	674

**CHAPTER 23 677****The eukaryotic gene: conserved exons and unique introns**

Organization of interrupted genes may be conserved	679
Genes show a wide distribution of sizes	682
One DNA sequence may code for multiple proteins	688
Exon sequences are conserved but introns vary	690
Genes can be isolated by the conservation of exons	691
How do interrupted genes evolve?	695

**CHAPTER 24 703****Gene numbers: repetition and redundancy**

Essential genes and total gene number	705
Globin genes are organized in two clusters	709
Unequal crossing-over rearranges gene clusters	711
Gene clusters suffer continual reorganization	715
Sequence divergence distinguishes two types of sites in DNA	717
The evolutionary clock traces the development of globin genes	718
Pseudogenes are dead ends of evolution	721
Genes for rRNA comprise a repeated tandem unit	723
An evolutionary dilemma: how are multiple active copies maintained?	729

<b>CHAPTER 25</b>		<b>733</b>
<b>Genomes sequestered in organelles</b>	Organelle genomes are circular DNA molecules that code for organelle protein	735
	The chloroplast genome has similarities to both prokaryotic and eukaryotic DNA	739
	The mitochondrial genome is large in yeast but small in mammals	741
	Recombination and rearrangement of organelle DNA	745
<b>CHAPTER 26</b>		<b>749</b>
<b>Organization of simple sequence DNA</b>	Highly repetitive DNA forms satellites	750
	Satellite DNAs often lie in heterochromatin	751
	Arthropod satellites have very short identical repeats	752
	Mammalian satellites consist of hierarchical repeats	754
	Evolution of hierarchical variations in the satellite	758
	The consequences of unequal crossing-over	760
	Crossover fixation could maintain identical repeats	762
	Minisatellites are useful for genetic mapping	763
<b>CHAPTER 27</b>		<b>767</b>
<b>The genome is packaged into chromosomes</b>	Condensing viral genomes into their coats	768
	The bacterial genome is a nucleoid with many supercoiled loops	772
	Loops, domains, and scaffolds in eukaryotic DNA	776
	The contrast between interphase chromatin and mitotic chromosomes	779
	The extended state of lampbrush chromosomes	782
	Transcription disrupts the structure of polytene chromosomes	784
	The eukaryotic chromosome as a segregation device	788
	Chromosome ends are special	791
<b>CHAPTER 28</b>		<b>797</b>
<b>Chromosomes consist of nucleosomes</b>	The nucleosome is the subunit of all chromatin	798
	The core particle is highly conserved	802
	DNA is coiled around the histone octamer	804
	Supercoiling and the periodicity of DNA	809
	The path of nucleosomes in the chromatin fiber	810
	Organization of the histone octamer	813
	Reproduction of chromatin requires assembly of nucleosomes	815
	Are nucleosomes arranged in phase?	819
	Are transcribed genes organized in nucleosomes?	822
	DNAase hypersensitive sites change chromatin structure	827
	Regulation of domains	831
	Gene expression is associated with demethylation	835
	Methylation is responsible for imprinting	839

**PART 7****Eukaryotic transcription and RNA processing 845****CHAPTER 29 847****Building the transcription complex:  
promoters, factors, and  
RNA polymerases**

Eukaryotic RNA polymerases consist of many subunits	849
Promoter elements are defined by deletions, point mutations, and footprinting	851
RNA polymerase I has a bipartite promoter	853
RNA polymerase III uses both downstream and upstream promoters	857
The basal transcription apparatus consists of RNA polymerase II and general factors	860
Promoters for RNA polymerase II promoters contain elements consisting of short sequences	864
Enhancers contain bidirectional elements that assist initiation	869
3' ends are generated by termination and by cleavage reactions	873

**CHAPTER 30 879****Regulation of transcription:  
factors that activate the  
basal apparatus**

Response elements identify genes under common regulation	880
Transcription factors bind DNA and activate transcription through independent domains	882
There are many types of DNA-binding domains	887
A zinc finger motif may provide a DNA-binding domain	889
Steroid receptors have domains for DNA binding, hormone binding, and activating transcription	893
Homeo domains may bind related targets in DNA	897
Helix-loop-helix proteins interact by combinatorial association	899
Leucine zippers may be involved in dimer formation	902
Speculations about the nature of gene activation	904

**CHAPTER 31 911****The apparatus for  
nuclear splicing**

Nuclear splicing junctions are interchangeable but are read in pairs	913
Nuclear splicing proceeds through a lariat	916
Small RNAs are required for splicing and form a spliceosome	919
Alternative splicing involves differential use of splicing junctions	929
<i>Cis</i> -splicing and <i>trans</i> -splicing reactions	932
Yeast tRNA splicing involves cutting and rejoining	935

Silent cassettes at <i>HML</i> and <i>HMR</i> are repressed	1067
Unidirectional transposition is initiated by the recipient <i>MAT</i> locus	1069
Regulation of <i>HO</i> expression	1071
Trypanosomes rearrange DNA to express new surface antigens	1074
Interaction of Ti plasmid DNA with the plant genome	1079
Selection of amplified genomic sequences	1087
Exogenous sequences can be introduced into cells and animals by transfection	1091

**PART 9****Genes in development 1101****CHAPTER 37 1103****Generation of immune diversity by gene reorganization**

Clonal selection amplifies lymphocytes that respond to individual antigens	1106
Immunoglobulin genes are assembled from their parts in lymphocytes	1108
The diversity of germ-line information	1115
Recombination between V and C genes generates deletions and rearrangements	1118
Allelic exclusion is triggered by productive rearrangement	1122
DNA recombination causes class switching	1124
Early heavy-chain expression can be changed by RNA processing	1127
Somatic mutation generates additional diversity	1128
T-cell receptors are related to immunoglobulins	1131
The major histocompatibility locus codes for many genes of the immune system	1135

**CHAPTER 38 1141****Gene regulation in development: gradients and cascades**

A gradient must be converted into discrete compartments	1143
Maternal gene products establish gradients in early embryogenesis	1146
Cell fate is determined by compartments that form by the blastoderm stage	1157
Complex loci are extremely large and involved in regulation	1166
The homeobox is a common coding motif in homeotic genes	1173

**CHAPTER 39 1181****Oncogenes: gene expression and cancer**

Transforming viruses may carry oncogenes	1185
Retroviral oncogenes have cellular counterparts	1190
Ras proto-oncogenes can be activated by mutation	1193
Insertion, translocation, or amplification may activate proto-oncogenes	1196
Loss of tumor suppressors causes tumor formation	1201
Immortalization and transformation	1205
Oncogenes code for components of signal transduction cascades	1208
Oncogenic variants of ras proteins are constitutively active	1213
Growth factor receptor kinases and cytoplasmic tyrosine kinases	1216
Oncoproteins may regulate gene expression	1223

<b>Epilogue</b>	Landmark shifts in perspectives	1231
<b>Glossary</b>		1235
<b>Index</b>		1259